Inhibition of elimination of caffeine by disulfiram in normal subjects and recovering alcoholics

The kinetics of caffeine elimination were investigated in 10 normal male subjects and in 11 recovering alcoholics before and during disulfiram dosing. In normal subjects the total body clearance of caffeine declined 30% (142 to 99 ml/min) at the maintenance dose of disulfiram, 250 mg/day, and 29% (161 to 114 ml/min) at the loading dose of 500 mg/day. In recovering alcoholics, the total body clearance decreased from 333 to 253 ml/min, a 24% change. The mean caffeine $t_{1/2}$ increased 39% and 34% in normal subjects after 250 and 500 mg disulfiram, respectively, and 29% in recovering alcoholics. The inhibition of caffeine elimination was moderate in most subjects. However, the clearance of caffeine decreased by ≥50% after disulfiram in three of the 11 recovering alcoholics. These patients may have an increased risk of cardiovascular and cerebral excitation associated with higher concentrations of caffeine, which could complicate withdrawal from alcohol. (CLIN PHARMACOL THER 1986;39:265-70.)

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It is estimated that 200,000 people are currently taking disulfiram (Antabuse; Ayerst Laboratories) as the aversion component of a comprehensive alcohol treatment program (Ayerst Laboratories: personal communication). The use of disulfiram in the treatment of alcoholism is based on the observation that disulfiram makes ethanol toxic to man. Consumption of alcohol by a person receiving disulfiram therapy results in a variety of unpleasant effects known as the acetaldehyde syndrome.[1] These symptoms typically include nausea, vomiting, and throbbing headache and are accompanied by elevated levels of acetaldehyde in the blood because of the inhibition of aldehyde dehydrogenase.[2] Disulfiram also inhibits the activity of other hepatic enzymes in vitro, including dopamine-β-hydroxylase,[3] ethylmorphine *N*-demethylase,[4] and xanthine oxidase.[5] Moreover, disulfiram prolongs the $t_{1/2}$ of a number of drugs including antipyrine,[6] warfarin,[7] phenytoin,[8] and thiopental[9] and diminishes the inductive effect of phenobarbital on cytochrome P-450.[4]

The metabolism of caffeine, a drug oxidized by liver microsomal enzymes, may be affected by disulfiram. Other drugs such as cimetidine,[10-12] idrocilamide,[13] and oral contraceptives[14] inhibit the elimination of caffeine. Coffee consumption is particularly high among recovering alcoholics[15,16] and its continued intake while they are taking disulfiram may result in higher concentrations of caffeine in the blood. This could complicate withdrawal from alcohol, because high concentrations of caffeine have been associated with increased irritability, insomnia, and symptoms of anxiety neurosis.[17,18]

Our investigation was undertaken to determine the effects of disulfiram, at the oral loading dose of 500 mg and maintenance dose of 250 mg, on the pharmacokinetics of caffeine in normal subjects and in recovering alcoholics.

METHODS

Subjects. Ten healthy, nonsmoking men 20 to 35 years old and 11 recovering alcoholics (nine men and two women) 19 to 35 years old consented to participate in this study. Alcoholics were in the second or third week of a rehabilitation program at a local hospital and all were habitual, heavy alcohol drinkers before entering the program. All subjects were healthy, with no evidence of liver or renal dysfunction based on clinical and laboratory tests including a complete blood count,

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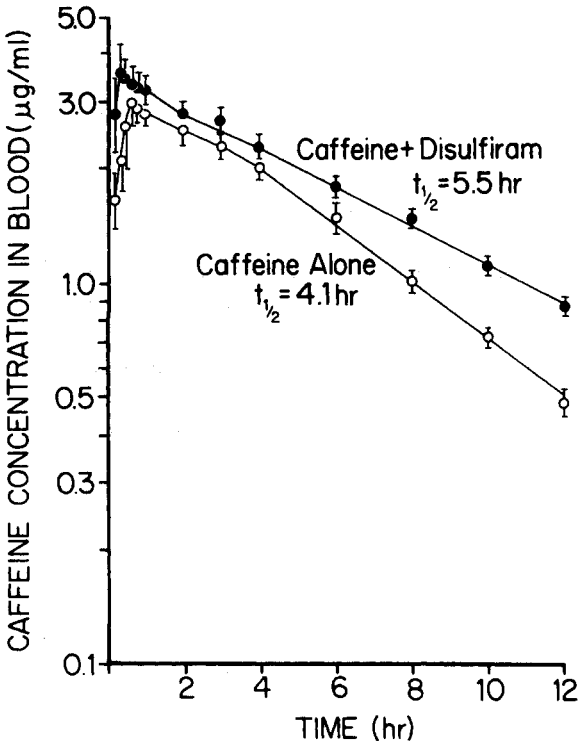

Fig. 1. Mean (± SE; n = 5) concentration of caffeine in the blood of normal subjects after caffeine, 200 mg po, before and on the fourth day of dosing with disulfiram, 500 mg/day.

urinalysis, and measurements of levels of serum electrolytes, glucose, albumin, total protein, alkaline phosphatase, SGOT, SGPT, γ-glutamyltransferase, lactate dehydrogenase, BUN, uric acid, creatinine, bilirubin, and cholesterol. Nine of the 11 alcoholics were smokers (20 to 50 cigarettes a day for at least 4 years). Patients D and K were nonsmokers and patients D and G were women. All participants abstained from methylxanthine-containing food and beverages 24 hours before and during the determination of caffeine kinetics. During the course of disulfiram dosing, normal subjects refrained from the ingestion of alcohol and methylxanthines. The recovering alcoholics had been free of medications for at least 10 days before the baseline determination of caffeine kinetics and during disulfiram dosing, except for the daily multiple vitamins they received throughout their hospitalization.

Study design. Caffeine (200 mg) was taken by mouth after an overnight fast as two Nodoz tablets (Bristol-Myers Co.) crushed and suspended in 100 ml tap water, followed by a rinse with 200 ml water. Blood samples (5 ml) were drawn through an indwelling intravenous catheter into tubes containing sodium heparin immediately before and 10, 20, 30, 40, and 50 minutes and 1, 2, 3, 4, 6, 8, 10, and 12 hours after caffeine dosing. The catheter was filled with heparinized saline solution between blood draws. This experiment provided the control or baseline pharmacokinetic data for each participant.

Normal subjects returned 5 days later to begin disulfiram dosing with either a maintenance dose of 250 mg/day or a loading dose of 500 mg po each day for 4 successive days. On the fourth day of disulfiram dosing, caffeine was administered 1 hour after disulfiram dosing and blood samples were drawn as described above. In alcoholic patients, studies of caffeine pharmacokinetics were repeated on the fifth day of 500 mg disulfiram dosing.

Caffeine assay. The concentration of caffeine in blood was determined the same day by HPLC.[19] Briefly, the procedure consisted of extracting caffeine from 1 ml samples of whole blood into 1-chlorobutane. Caffeine and the internal standard (8-chlorotheophylline) were separated on a reverse-phase column (5 μm Nucleosil C-18, 250 × 4.6 mm; Alltech) by use of a mobile phase of pH 5.5 acetate buffer (10 mmol/L)/acetonitrile/methanol (80/10/10) at a flow rate of 1.2 ml/min. Absorbance was monitored at 273 nm. Standard curves were prepared daily from blank blood spiked with caffeine over a concentration range of 0.05 to 10 μg/ml.

Data analysis. The terminal rate constant of caffeine (β) was determined by linear regression analysis of the logarithm of the blood caffeine concentration-time relationship from 2 to 12 hours (4 to 12 hours for subjects 1 and 2). The $t_{1/2}$ was calculated as: $t_{1/2} = 0.693/\beta$. The blood AUC from 0 to 12 hours was calculated by the trapezoidal rule, and the AUC from 12 hours to infinity was estimated as the blood concentration at 12 hours divided by β. Total body clearance (CL) of caffeine was calculated as: CL = Dose/AUC. The fraction of the dose absorbed was assumed to be one.[20] The apparent volume of distribution (V_{area}) was calculated as: V_{area} = Dose/(β · AUC). The maximum concentration of caffeine in the blood (C_{max}) and time to reach C_{max} (t_{max}) were determined by inspection of the data.

Student's t test for paired samples was used for statistical comparison of baseline caffeine values and values after disulfiram. Because our a priori hypothesis was that disulfiram inhibited the elimination of caffeine, a one-tailed test was used for CL and $t_{1/2}$, while a two-tailed test was used for V_{area}, t_{max}, and C_{max}.[21] Mean $t_{1/2}$ was calculated as the harmonic mean by dividing 0.693 by the mean β. The P values for $t_{1/2}$ were calculated by use of the values for β. The differences between the pharmacokinetic data before and after di-

sulfiram for the 250 mg group were compared with those of the 500 mg group by the unpaired t test.

RESULTS

The profiles of the caffeine concentration-time relationship before and during disulfiram dosing for normal subjects and alcoholics are shown in Figs. 1 and 2, respectively. The corresponding pharmacokinetic data are summarized in Tables I and II. In most participants the caffeine C_{max} (2 to 6 μg/ml) occurred rapidly (t_{max} = 10 to 180 minutes), and then the concentration of caffeine slowly declined over a period of several hours. Disappearance of caffeine from blood followed apparent first-order kinetics over the concentration range assayed. The average $t_{1/2}$ for caffeine before disulfiram was 4.1 hours for the normal subjects, which is in agreement with values obtained previously in our laboratory.[22]

Oral doses of disulfiram, 250 or 500 mg/day, for 4 or 5 days inhibited the elimination of caffeine in all participants. The mean CL of caffeine decreased 30% (142 to 99 ml/min; $P < 0.005$) and the mean $t_{1/2}$ increased 39% (4.1 to 5.7 hours; $P < 0.01$) in normal subjects who received 250 mg disulfiram. In normal subjects who received 500 mg disulfiram, the mean CL decreased 29% (161 to 114 ml/min; $P < 0.005$) and mean $t_{1/2}$ increased 34% (4.1 to 5.5 hours; $P < 0.005$). In alcoholics who received 500 mg disulfiram, the mean CL of caffeine decreased 24% (333 to 253 ml/min; $P < 0.001$) and mean $t_{1/2}$ increased 29% (2.1 to 2.7 hours; $P < 0.002$). No statistically significant changes in t_{max} were observed after disulfiram dosing. The C_{max} was significantly higher after disulfiram in only the normal subjects given 500 mg disulfiram. The V_{area} decreased slightly in all groups, but was statistically significant ($P < 0.05$) only for the healthy subjects given 250 mg disulfiram. There was no significant difference between the effect of the maintenance dose of 250 mg disulfiram and the loading dose of 500 mg disulfiram on inhibition of caffeine elimination in normal subjects.

DISCUSSION

Our results demonstrate that the elimination of caffeine is inhibited by therapeutic doses of disulfiram in both normal subjects and in recovering alcoholics. The t_{max} was not significantly changed by disulfiram, indicating that caffeine absorption was not altered. The elimination of caffeine was greatly inhibited in one normal subject (No. 2). His CL declined 81% (67 to 13 ml/min) and $t_{1/2}$ increased 431% (6.7 to 28.9 hours) after disulfiram. We have no explanation for the exaggerated effect of disulfiram on this individual. It should be noted that before disulfiram dosing this subject was the slowest metabolizer of caffeine of all subjects tested.

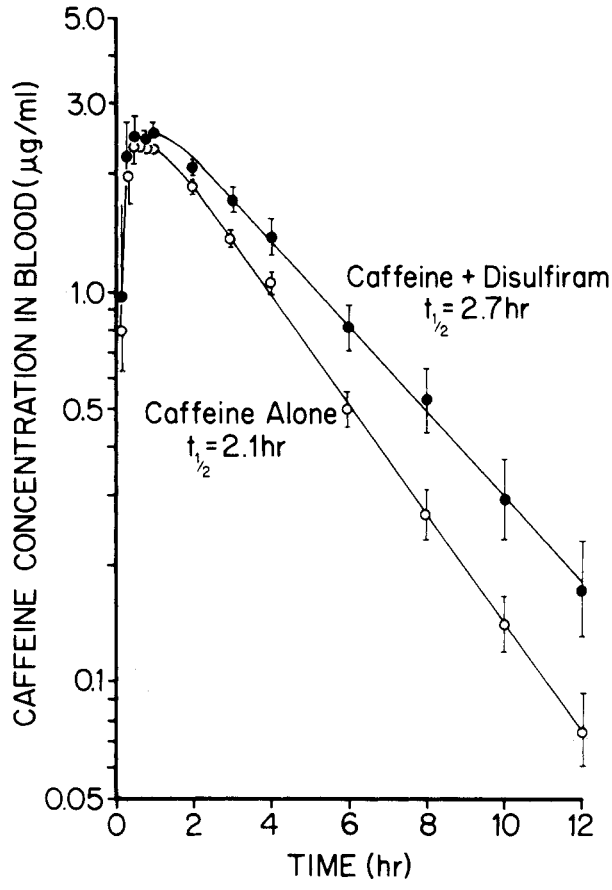

Fig. 2. Mean (±SE; n = 11) concentration of caffeine in the blood of recovering alcoholics after caffeine, 200 mg po, before and on the fifth day of dosing with disulfiram, 500 mg/day.

A separate study was performed to ensure that abstinence from methylxanthines or alcohol (most normal subjects in this study were moderate drinkers) did not affect caffeine elimination. Caffeine kinetics were measured in five normal subjects before and after they abstained from alcohol and methylxanthines for 1 week. In these subjects there was no significant difference in any pharmacokinetic parameter before and after abstinence (data not shown). Thus the inhibition of caffeine elimination in our healthy subjects was attributed to disulfiram therapy.

The elimination of caffeine in hospitalized alcoholics was also inhibited by disulfiram. Drug interaction studies in the alcoholic population are more difficult to

Table I. Effect of disulfiram on caffeine elimination in normal subjects

Subject No.	CL (ml/min)		$t_{1/2}$ (hr)		V_{area} (L)		C_{max} (μg/ml)		t_{max} (hr)	
	Pre DS	*Post DS*	*Pre DS*	*Post DS*	*Pre DS*	*Post DS*	*Pre DS*	*Post DS*	*Pre DS*	*Post DS*
250 mg DS										
1	112	80	5.0	6.4	48.9	44.2	2.9	3.9	2.00	0.83
2	67	13	6.7	28.9	38.6	33.2	3.9	5.7	3.00	0.33
3	217	172	3.0	3.8	55.6	57.0	4.3	3.3	0.33	0.33
4	167	143	3.7	4.1	53.0	50.5	3.1	3.3	0.67	0.83
5	145	85	3.8	5.7	47.8	42.1	3.2	6.1	1.00	0.33
$\bar{X}$	142	99	4.1	5.7	48.8	45.4	3.5	4.5	1.40	0.66
SE	25	27	*	*	3.1	4.0	0.3	0.6	0.49	0.14
%Change	−30		39		−7.0		29		−53	
P value	<0.005		<0.01		<0.05		NS		NS	
500 mg DS										
6	172	94	4.2	7.1	62.2	58.1	2.4	3.4	0.67	1.00
7	137	98	4.7	6.4	50.4	54.4	4.4	5.5	0.50	0.17
8	141	99	4.3	6.1	52.8	44.7	3.6	4.6	0.83	0.67
9	180	125	3.6	4.2	56.5	45.5	2.9	4.4	0.83	0.33
10	173	154	4.0	4.6	59.3	61.2	2.7	2.8	1.00	0.83
$\bar{X}$	161	114	4.1	5.5	56.2	52.8	3.2	4.1	0.77	0.60
SE	9	11	*	*	3.4	3.3	0.4	0.5	0.08	0.15
%Change	−29		34		−6.0		28		−22	
P value	<0.005		<0.005		NS		<0.025		NS	

DS = Disulfiram; NS = not significant.
*Harmonic mean.

Table II. Effect of 500 mg disulfiram on caffeine elimination in alcoholics

Patient	CL (ml/min)		$t_{1/2}$ (hr)		V_{area} (L)		C_{max} (μg/ml)		t_{max} (hr)	
	Pre DS	*Post DS*	*Pre DS*	*Post DS*	*Pre DS*	*Post DS*	*Pre DS*	*Post DS*	*Pre DS*	*Post DS*
A	367	332	2.6	2.9	95.2	82.4	2.1	2.0	1.00	1.00
B	283	273	2.8	2.8	68.4	65.2	2.3	2.5	0.50	1.00
C	346	288	2.0	2.2	59.0	54.9	3.7	4.6	0.25	0.25
D*†	258	116	2.4	5.2	54.1	52.1	4.2	4.0	0.50	0.25
E	375	232	1.9	2.5	65.2	51.6	3.6	4.6	0.25	0.41
F	405	309	2.1	3.1	75.8	81.9	2.9	1.9	0.33	1.00
G†	319	287	2.0	2.4	54.0	59.9	2.6	3.1	1.00	0.33
H	370	335	1.5	1.6	49.3	46.7	2.5	2.5	0.67	0.67
I	332	323	2.2	2.2	62.0	62.2	2.3	2.4	0.67	0.67
J	370	174	1.7	3.4	53.7	51.9	2.5	3.4	1.00	0.50
K*	243	115	2.9	6.1	60.2	61.1	2.4	3.5	1.00	0.50
$\bar{X}$	333	253	2.1	2.7	63.4	60.9	2.8	3.1	0.65	0.60
SE	16	25	‡	‡	3.9	3.6	0.2	0.3	0.09	0.09
%Change	−24		29		−4.0		11		−7.7	
P value	<0.001		<0.002		NS		NS		NS	

DS = Disulfiram; NS = not significant.
*Nonsmoker.
†Female.
‡Harmonic mean.

control than are those in normal subjects. During the first few days, patients admitted to a hospital rehabilitation unit frequently are given diazepam or phenobarbital (known to induce metabolic enzymes) to ease withdrawal from alcohol and to prevent seizures. In addition, most recovering alcoholics, including nine of the 11 patients we studied, smoke cigarettes, which is known to increase the rate of elimination of caffeine.[23]

Indeed, caffeine CL in the alcoholics who smoked was significantly faster than that in nonsmoking subjects. Although the inhibitory effect of disulfiram was modest overall among the alcoholics studied, the caffeine $t_{1/2}$ increased twofold or more in three patients, two of whom were the only nonsmoking alcoholics in the study.

It is not known whether smoking alters the metabolism of disulfiram. A recent study by Faiman et al.[24] showed marked intersubject variability in plasma concentrations of disulfiram and its metabolites in alcoholics. Because both disulfiram and some of its metabolites are enzyme inhibitors,[25] variation in the metabolism of disulfiram may contribute to variability in its inhibitory effect.

It has been known for over a decade that acute ethanol dosing inhibits[25] and chronic ethanol dosing induces[26,27] drug metabolism. It is possible, therefore, that caffeine CL in recovering alcoholics may be declining during their period of withdrawal. To our knowledge, the time course of loss of enzyme induction after the end of alcohol ingestion in humans is not known. However, studies in laboratory animals have shown that enzyme activity declines to baseline values 7 days after withdrawal of ethanol.[28,29] Thus it seems unlikely that the change in caffeine CL in recovering alcoholics in our study was a result of decreased enzyme induction, because the baseline pharmacokinetics were determined at least 10 days after the last ingestion of ethanol.

Because caffeine is eliminated by biotransformation,[30,31] it is probable that disulfiram, a known inhibitor of liver microsomal reactions, reduces the elimination rate of caffeine by inhibiting its metabolism in liver microsomes. The major pathway of biotransformation of caffeine is *N*-demethylation in the liver.[32,33] Caffeine and its metabolites have also been reported to be substrates for xanthine oxidase,[34,35] an enzyme that is inhibited by disulfiram.[5] Allopurinol, another inhibitor of xanthine oxidase, moderately decreases (23%) the CL of theophylline, whose metabolism is similar to that of caffeine.[36] To our knowledge, the effect of allopurinol on caffeine metabolism in vivo has not been studied. Hence the impact of disulfiram inhibition of xanthine oxidase on elimination of caffeine is not clear.

Higher concentrations of caffeine in blood can lead to increased anxiety, nervousness, and insomnia,[17,18,37] symptoms that may complicate the therapy and rehabilitation of the recovering alcoholic, especially the adjustment to abstinence. Such patients may relapse and resume the consumption of alcohol for its sedative or tranquilizing effects. Cardiovascular disease associated with chronic consumption of alcohol[38] may be exacerbated by caffeine. Extrasystoles[39] and myocardial infarction[40] occur more frequently in heavy coffee drinkers. Patients with a history of heart disease are especially susceptible to the arrhythmogenic effects of caffeine.[41]

In summary, the elimination of caffeine is impaired by disulfiram therapy. This may lead to higher concentrations of caffeine in tissues, which may predispose to cerebral and cardiac excitation, thereby complicating withdrawal from alcohol.

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